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NUTRITION REVIEWS

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NUTRITION REVIEWS

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NUTRITION AND FOOD SUPPLY IN GERMANY AND AUSTRIA

The formation of the United Nations Commission on Food and Agriculture hopefully represents tangible evidence of an increasing awareness of the importance of food production and distribution in maintaining the peace of the world. This is expressed in the First Report of the Interim Commission on Food and Agriculture (1944):

"In the struggle for food, mankind has been indifferently successful. If millions have enough, more millions have too little, and many starve. This had been thought to be inevitable, but we now know that it is not. Recent discoveries and developments have made it possible under certain conditions for all men and all nations to achieve freedom from hunger, which is the first step toward freedom from want. Indeed, we can now expect to do much more than be free from hunger. The way is open to move toward new levels of well-being which men have hitherto thought unattainable."

Warlike and aggressive peoples require good nutrition to attain their ends but of more importance now is the fact that political unrest, riots, and even war may result from an insufficient availability of food. The United States Army has recognized the importance of food in the management of defeated Germany and Austria. Great foresight has been shown in the policy of carefully rebuilding a democratic Germany unable again to wage wars of aggression, and at the same time preventing as far as possible political unrest and riots by an equitable distribution of the food resources available. In doing this, the Army has utilized to the fullest its facilities in nutrition as represented by the Nutrition Division of the Preventive Medicine Service, Office of The Surgeon General, the nutrition service which it has established in the Public Health Branch of Military Government, and such other agencies in Military Government as the Food and Agriculture Branch and Economics Division. Experts in these fields have been called upon either as members of the Army or as civilian consultants, and a combined food and nutrition program has evolved which it is hoped will expedite the Army's fundamental policy of equitable distribution of available food.

As an integral part of this program, surveys of the nutritional status of the civilians of occupied Germany and Austria were begun shortly after the end of the war. At the present writing, such studies have been made repeatedly in all the large cities and many of the smaller ones in the zone occupied by American forces. It is planned that surveys continue to be repeated in each city every three months or oftener.

Six nutrition survey teams have been set up for United States, occupied Germany, and Austria, each consisting of a nutrition officer trained in taking nutrition histories, a clinician to judge the nutritional status of individuals, and a laboratory technician. When possible a second nutrition officer has been added to the team. A compact and practical mobile laboratory, as devised by the Army's Nutrition Laboratory, is furnished to each team. Until recently, blood hemoglobin and serum protein estimations represented the extent of the laboratory work, but arrangements have now been completed whereby small blood samples may be sent to a central laboratory for measurements of serum ascorbic acid, vitamin A, carotene, and alkaline phosphatase.

In each city, with the help of the Army's military government, and with the aid of civilian public health and food rationing authorities, a representative and, as far as

possible, a statistically valid sample of the population is selected, according to age, sex, and food ration categories. Those chosen (250 to 300 per day per team) come to a central examining place where the age, sex, height, and weight of each are recorded. A brief clinical examination is performed on all subjects to ascertain the presence or absence of certain specified symptoms and signs suggestive of nutritional deficiency. Ten per cent of the individuals are then questioned concerning their food intake. This is compared with the planned ration to determine existing deficiencies or supplementation. Blood hemoglobin and serum proteins are measured on approximately half of those examined. These careful studies are supplemented by weight measurements made by the Germans themselves on much larger but less carefully selected groups of persons. Upwards of 100,000 persons are weighed each month. These weighings, which are repeated at monthly intervals in nearly all of the communities in the American zone, permit a rapid assessment of the trends in the general nutrition situation.

From the clinical examination, laboratory studies, diet histories, and weight records, an estimate of the effect of previous food intake is made. With this as a background, the adequacy or extent of inadequacy of food being eaten at the time of survey can be estimated, prophesies made of the time required for specific deficiencies to occur, and recommendations formulated of food requirements of the area concerned. Reports made from the areas studied have been used by the Food and Agriculture Divisions, in conjunction with their own reports on local food production and food supplies, to decide upon the movements of food from surplus areas to those unable to meet their ration. The Nutrition Division of The Surgeon General's Office has furnished plans and direction for these surveys as well as a panel of experts to aid with the surveys and their interpretation.

As well as the practical political and economic findings of these surveys, they offer an excellent opportunity to assess methods of performing nutrition surveys. Thus, one may expect from the discussion and suggestions of the nutritionists conducting the surveys that there will arise standardized methods of survey technic. It is hoped that the results of the individual surveys as well as of the compiled and analyzed results will become a part of the medical nutrition literature in the near future. However, certain of the preliminary findings can be mentioned here.

Germans and Austrians, who prior to the war were generally well over American standards for weight, lost considerable weight during war rationing. In general, this did not reach the degree of starvation and nutritional deficiencies reported from Holland (*Nutrition Reviews* **3,** *225 (1945)*). However, in the larger cities, especially the American occupied sectors of Berlin and Vienna, where nutrition among the poor has never been satisfactory, surveys made immediately after occupation of the areas by American troops showed reductions of weight of the civilians to be extreme. In fact, 48 per cent of the Viennese were more than 10 kg. below United States standards in weight. Nutritional edema and hypoproteinemia, in small numbers of cases, were present in both cities, although, as in the remainder of the occupied territory, little in the way of signs suggestive of specific vitamin deficiencies was seen. Anemia was not found to be prevalent.

That more signs and symptoms indisputably attributable to vitamin deficiencies were not seen in the face of the deficient diets deserves comment. The greatest deficit in most cases was of calories, with protein next. Because of the reduced caloric intake, and probable reduced metabolism, it seems likely that requirements of at least some of the vitamins were reduced. Furthermore, in most instances, unrefined

food was eaten, thus furnishing more vitamins than one might expect.

The nutritional situation described was brought about in part by dietary restrictions imposed by the Germans themselves before the end of the war, and in part by further restrictions imposed by necessity after the cessation of hostilities. During the past fall and winter the situation has shown considerable improvement in regard to caloric intake.

During January the "normal adult consumer" in the U. S. zone actually received about 1900 calories, of which 1600 derived from rationed food and 300 from various other sources (unrationed items, private stocks, etc.). The other ration categories (children, heavy workers, etc.) received greater or lesser amounts of food which appeared in general to be proportionate to their needs. Thus eight months after VE day the caloric intake of the German population in the American zone had been restored to a level sufficient to prevent hardship. The average weights of the populace confirm the conclusion that nearly adequate amounts of food were being consumed; indeed, most of the ration categories showed an increase in weight as compared with previous months. The only persons who clearly required more calories than they were receiving were the heavy workers (estimated consumption 2560 calories).

It thus seems evident that in January, and there are indications that the same was true at least through February and March, the German populace in the American zone was being fed, if not abundantly, at least adequately to prevent deterioration. Judging from other allied reports, the same conclusion applies to the British zone. Whether or not the supplies of food will continue at the present level is, of course, a matter of concern. Should food supplies be decreased so that the total calories consumed are below 1500, a serious condition would develop if such low levels were prevalent for any length of time.

For further details of the situation as it existed earlier, the reader is referred to two reports in the recent literature. One concerns a study made during July, 1945 in Stuttgart, a representative urban area in the American zone of occupation (J. M. Ruffin and C. E. French, *South. Med. J.* **39,** *112 (1946)*). The second article reports the situation as it existed in September, 1945 in the British zone of Vienna (M. Pyke, *Brit. Med. J.* **2,** *839 (1945)*).

It may be hoped that the experiences gained from the nutrition surveys under the direction of both the United States Army and other organizations throughout the world will become a basis for similar surveys organized by the United Nations Commission on Food and Agriculture. Facts gained in this way should become important in guiding the movement of food between nations.

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PRESENT KNOWLEDGE OF THE VITAMIN B-COMPLEX IN HUMAN NUTRITION (PART II)

There is no definite knowledge concerning the signs and symptoms of pyridoxine deficiency in man. Therapeutic trial of this vitamin has been made in patients with muscular weakness (*Nutrition Reviews* **1,** *15 (1942)*), with epilepsy (*Ibid.* **1,** *26 (1942)*), with certain types of dermatitis (*Ibid.* **1,** *157, 370 (1943)*), and with nausea and vomiting of pregnancy (*Ibid.* **2,** *182 (1944)*; **4,** *170 (1946)*). The results have been inconclusive or disappointing.

Rats deficient in pyridoxine show a

characteristic dermatitis, convulsive (epileptoid) seizures (*Nutrition Reviews* **1,** *26* (*1942*)), and muscular weakness (*Ibid.* **2,** *261* (*1944*)) as well as impaired growth. Dogs and swine develop a hypochromic anemia (*Ibid.* **3,** *29* (*1945*)) and swine develop in addition epileptiform seizures and abnormalities of gait accompanied by lesions of the nervous system (*Ibid.* **3,** *269* (*1944*)).

A great deal of information has been accumulated concerning the function of pyridoxine and related compounds (pyridoxal and pyridoxamine) both in bacterial enzyme systems and in experimental animals. E. E. Snell and co-workers have shown that certain bacteria which ordinarily require pyridoxine will grow without it when adequate alanine is present in the medium (*Nutrition Reviews* **2,** *99* (*1944*)). Under these conditions it appears that the microorganisms do not synthesize pyridoxine but actually do not require it (*Ibid.* **3,** *343* (*1945*)). From the work of I. C. Gunsalus and co-workers, phosphorylated pyridoxal appears to be the coenzyme for various decarboxylases (*Ibid.* **3,** *72, 343* (*1945*)) and there is evidence that it is also the coenzyme for certain transaminases (F. Schlenk and E. E. Snell, *J. Biol. Chem.* **157,** *425* (*1945*)) and H. C. Lichstein, I. C. Gunsalus, and W. W. Umbreit, *Ibid.* **161,** *311* (*1945*)). S. Lepkovsky and collaborators have shown that abnormally large amounts of xanthurenic acid (resulting from the metabolism of tryptophane) appear in the urine of pyridoxine deficient rats (*Nutrition Reviews* **3,** *72* (*1945*)). The precise function of pyridoxine in the metabolism of tryptophane is not entirely clear but it has been suggested (*Ibid.* **3,** *343* (*1945*)) that the normal metabolism of this amino acid is regulated by pyridoxine and leads to compounds other than xanthurenic acid. According to this postulate, xanthurenic acid is not an intermediate but rather a product of abnormal metabolism.

Pantothenic acid was at one time offered to the public as a specific against human achromotrichia (graying of the hair). Carefully controlled observations, however, have shown that it has little or no value for this purpose (*Nutrition Reviews* **1,** *365* (*1943*); **2,** *90* (*1944*)). Other uses for this vitamin in human beings have not received serious consideration and the nature of pantothenic acid deficiency in man is completely unknown.

In the rat and in many other animals omission of pantothenic acid from the diet results in very striking graying of the hair and in failure of growth. In addition to these deficiency signs, hemorrhage and necrosis of the adrenals, anemia and leukopenia, and porphyrin-staining of the fur and whiskers have been observed in the rat. In the dog a deficiency of pantothenic acid manifests itself by a severe hypoglycemia, by convulsions, coma, fatty livers, mottled thymus, and gastrointestinal disorders including gastritis, enteritis, and intussusception; the motility of the intestinal tract and the digestion and absorption of carbohydrate and protein are decreased also (*Nutrition Reviews* **2,** *85, 298* (*1944*)). A mild anemia has been reported. Swine deficient in this vitamin show failure of growth, loss (but not graying) of hair, a cough, excessive nasal secretion, changes in the tongue, a mild anemia, diarrhea associated with an ulcerative colitis, and an abnormality of gait accompanied by lesions of the sensory neurons (*Ibid.* **2,** *125* (*1944*); **3,** *269* (*1945*)). Pantothenic acid in excess of the recognized daily requirements appears to increase the hatchability of eggs and increase the litter size in rats and mice (*Ibid.* **1,** *413* (*1943*)). Since the relative sizes of the brain and heart were decreased in the offspring in these experiments it is not certain that the effect is a desirable one.

Little is known about the actual function of pantothenic acid in the animal body. From the fact that it appears to be bound to protein in the blood it has been postulated that it is a component of an enzyme system and from its disappearance from blood fol-

lowing a test meal of glucose it has been suggested further that it participates in glucose utilization (*Nutrition Reviews* **2,** *21* (*1944*)). A promising lead has been furnished by E. P. Ralli and associates who have shown that the achromotrichia which develops in rats as a result of pantothenic acid deficiency may be overcome by removal of the adrenal glands (*Ibid.* **4,** *84* (*1946*)). From these results it appears possible, although not proved, that the effect of pantothenic acid on the formation of hair pigment is mediated by the adrenals.

Attempts have been made to induce biotin deficiency in man by the inclusion of large amounts of raw egg white in a diet low in the vitamin. The signs and symptoms reported by one group of investigators were a peculiar grayish pallor of the skin, atrophy of the lingual papillae of the tongue, mild depression followed by extreme lassitude and sleeplessness, loss of appetite, electrocardiographic changes similar to those found in thiamine deficiency, and slight anemia. Treatment with a biotin concentrate brought about prompt relief (*Nutrition Reviews* **1,** *18* (*1942*)). Other investigators have failed to observe deficiency manifestations following the feeding of unheated egg white (*Ibid.* **1,** *280* (*1943*); **2,** *345* (*1944*)). There remains, therefore, considerable uncertainty as to the ease of production of biotin deficiency in man and its exact nature.

For purposes of therapy, attempts have been made to produce rather than to cure biotin deficiency in man. This rather anomalous situation has resulted from the suggestion, now completely disapproved, that a biotin deficiency might be beneficial to individuals with cancer. Following the observations that some cancerous tissues contain abnormally large amounts of biotin (*Nutrition Reviews* **1,** *51* (*1942*)) and that the administration of this vitamin to rats receiving butter yellow appeared, under certain conditions to increase the incidence of hepatic tumors, attempts were made to treat patients by inducing a biotin deficiency. Some of these clinical trials have been reviewed in this journal (*Ibid.* **1,** *280* (*1943*); **2,** *345* (*1944*)). Preliminary results interpreted as slightly encouraging have been followed, on more adequate test, by complete failure.

Biotin deficiency has been produced in experimental animals by three methods. In some species, such as the chick and monkey, feeding a highly purified diet suffices. In others, notably the rat, there must be included in the diet raw egg white which prevents the absorption of biotin, or some bacteriostatic agent such as a sulfonamide (*Nutrition Reviews* **2,** *221* (*1944*)) which acts, presumably, by preventing the synthesis of biotin by the bacteria of the gastrointestinal tract. The ingredient of egg white which is active in preventing the absorption of biotin has been shown to be a basic protein and has been named "avidin." It has the property of combining stoichiometrically with biotin to form an unabsorbable complex.

The usual manifestations of biotin deficiency in experimental animals are dermatitis and loss of hair. The pruritic exfoliative dermatitis which develops in young rats is accompanied by an abnormal posture and gait (*Nutrition Reviews* **1,** *190* (*1943*)) there being an excessive elevation and rounding of the spine in the lumbosacral region and a tendency to step off the top of the digits. In chicks the dermatitis is accompanied by perosis or "slipped tendon" (*Ibid.* **2,** *50* (*1944*)). In monkeys, loss of hair is a prominent deficiency sign and dermatitis is observed in severe cases (*Ibid.* **3,** *212* (*1945*)). Biotin appears to be necessary for reproduction in the rat and possibly in other species (*Ibid.* **3,** *343* (*1945*)).

A small amount of evidence which suggests that biotin may function in the utilization of lactate and pyruvate in the animal body has been presented (*Nutrition Reviews* **2,** *21* (*1944*); **3,** *32* (*1945*)).

The nomenclature for Lactobacillus casei factor, a relatively new member of the vita-

min B-complex, is still somewhat controversial but the principal impediment to our understanding in this field has been a pointless insistence on the dissimilarity of actually very similar compounds. The names most frequently used are "L. casei factor," "folic acid," "vitamin Bc," and "vitamin M." On the basis of present evidence it appears that these names all refer to a single vitamin. This vitamin undoubtedly exists in nature, in several, perhaps many, closely related forms but this situation is hardly a unique one in this or other biochemical fields (consider vitamin A, vitamin D, vitamin K, penicillin). In so far as information is at present available the compound isolated from liver (*Nutrition Reviews* **3,** *131* (*1944*)) and later synthesized (*Ibid.* **4,** *11* (*1946*)) is the most active form. The two compounds isolated from yeast (*Ibid.* **2,** *131* (*1944*); **4,** *15* (*1946*)) and the one isolated from a fermentation residue (*Ibid.* **4,** *15* (*1946*)) appear to be conjugates or possibly, in some cases, derivatives of some other type. The compound which occurs in spinach (*Ibid.* **2,** *131* (*1944*)) has not been isolated but from the properties of its concentrates it will most likely prove to be a form of the same vitamin.

This new vitamin has been shown to be an extremely active hematopoietic factor in man (*Nutrition Reviews* **4,** *11*, *102* (*1946*)). It appears to be well established that it is effective in the treatment of sprue and pernicious anemia and probably in the treatment of dietary macrocytic anemia and the macrocytic anemias of pellagra, of pregnancy, and of infants. There is a suggestion that it may be beneficial in the leukopenia encountered following radiation therapy. It is as yet too early to say whether it will benefit all patients with these various dyscrasias and whether normal blood pictures will be attained and maintained through this type of therapy, but the responses reported to date have been encouraging.

The clinical trial of the L. casei factor in anemia and in leukopenia and granulocytopenia was clearly indicated from its value in experimental animals. A. G. Hogan and collaborators and the Detroit group had demonstrated the value of "vitamin Bc" isolated from liver, in preventing and curing dietary anemia in chicks (*Nutrition Reviews* **2,** *54* (*1944*)); F. S. Daft and W. H. Sebrell had shown that the same material and another crystalline form of the vitamin were effective in correcting sulfonamide induced leukopenia, granulocytopenia, and anemia in rats (*Ibid.* **2,** *103* (*1944*)); and P. L. Day and collaborators had used a crystalline preparation of the vitamin successfully in the treatment of monkeys suffering from "vitamin M" deficiency (*Ibid.* **3,** *351* (*1945*); **4,** *102* (*1946*)).

Other signs of L. casei factor deficiency in experimental animals which have been reported are achromotrichia and porphyrin-staining of fur and whiskers in the rat (*Ibid.* **2,** *221* (*1944*)), diarrhea, oral lesions, and edema in the monkey (*Ibid.* **4,** *11* (*1946*)), impairment of the response to estrogens in the chick (*Ibid.* **3,** *308* (*1945*)), and decreased resistance to malarial infection, also in the chick (*Ibid.* **3,** *345* (*1945*)).

The function of L. casei factor in the bacterial cell and in the animal body is at best incompletely understood. The only clue so far is that furnished by J. L. Stokes (*J. Bact.* **48,** *201* (*1944*)). It had been shown previously that certain bacteria which normally require this vitamin could grow without it when a comparatively large amount of thymine (a component of one type of nucleic acid) was added to the medium. Stokes demonstrated that the bacteria which were grown in this way were devoid of L. casei factor and suggested that the function of the vitamin in these organisms was to assist in the synthesis of thymine. T. D. Spies, C. F. Vilter, J. K. Cline, and W. B. Frommeyer (*South. Med. J.* **39,** *269* (*1946*)) have reported that one

patient treated with very large amounts of thymine recovered from pernicious anemia. It is premature to attempt to appraise these suggestions at this time.

The clinical use of choline has been restricted almost entirely to treatment of liver cirrhosis and in general the results have been mildly encouraging. In a study of the use of choline alone, with no other change in the diet, no cases of clinical improvement which were attributable to this therapy were noted (*Nutrition Reviews* **2,** *314* (*1944*)). Where choline has been given in conjunction with a diet high in vitamins, protein, and calories, however, there appears to have been a definite beneficial effect of the choline (in addition to a beneficial effect of this type of diet without the added choline). The first few of these favorable reports have been reviewed in this journal (*Ibid.* **1,** *88* (*1943*); **2,** *314* (*1944*); **3,** *158* (*1945*)). The data presented suggest that a choline deficiency may be contributory to human liver cirrhosis but that other as yet unidentified dietary factors are involved also.

In most species of animals, a deficiency of choline leads to fatty livers. In young rats, acutely deficient, this is accompanied by hemorrhagic degeneration of the kidneys and hemorrhage into the eyeballs and other organs of the body (*Nutrition Reviews* **1,** *156*, *168* (*1943*); **2,** *314* (*1944*)). Older rats, and young rats which survive the acute stage, develop liver cirrhosis (*Ibid.* **1,** *88* (*1943*); **2,** *314*, *340* (*1944*); **3,** *122* (*1945*)). Choline deficiency in chicks and young turkeys manifests itself as perosis or "slipped tendon" (*Ibid.* **2,** *50*, *314* (*1944*)) and by decreased egg production and a high mortality rate (*Ibid.* **2,** *358* (*1944*)). Rabbits deficient in choline develop fatty livers and liver cirrhosis (*Ibid.* **2,** *314* (*1944*)). Weanling puppies deficient in this vitamin may die within three weeks with severe fatty infiltration of the liver (*Ibid.* **3,** *124*, *261* (*1945*)) while for older dogs a deficiency state characterized by loss of weight, moderate anemia, dermal and peptic ulcers, and a fatty cirrhotic liver (*Ibid.* **2,** *298* (*1944*)) has been described. The hamster appears to require choline for successful lactation (*Ibid.* **2,** *361* (*1944*)).

Choline deficiency in most experimental animals is accompanied by at least some degree of protein deficiency or, more specifically, by a deficiency of methionine, one of the essential amino acids. The necessity of this relationship arises because the rat and apparently most other animals are able to synthesize choline from methionine plus glycine or serine (*Nutrition Reviews* **2,** *358* (*1944*)). In practice, the limiting one of these is methionine and, therefore, in order to attain the desired choline deficiency we must accept, in most experimental animals, methionine deficiency as well. Our knowledge concerning choline deficiency has been obtained by comparing animals deficient in both choline and protein (or methionine) with animals receiving a similar diet with added choline.

One biochemical defect in choline deficiency appears to be insufficient formation of phospholipid to accommodate fat metabolism or transport (choline being one component of certain phospholipids). Other possible biochemical defects are insufficient methyl groups to form other needed compounds and inadequate formation of acetylcholine (*Nutrition Reviews* **2,** *275* (*1944*)).

The position of inositol as a dietary essential now appears to be assured but little is known concerning its value in human nutrition. A report has appeared which indicates that, under certain conditions, inositol is a lipotropic factor in man, that is, it is effective in preventing or curing fatty livers (*Nutrition Reviews* **2,** *163* (*1944*)).

Perhaps the most thoroughly explored use of inositol in experimental animals is as a lipotropic factor. There appears to be general agreement among investigators in this field that inositol has at least a synergistic action with choline in reducing the

level of fat in fatty livers (*Nutrition Reviews* **2,** *163, 302* (*1944*); **3,** *88* (*1945*); C. H. Best, C. C. Lucas, J. M. Patterson, and J. H. Ridout, *Science* **103,** *12* (*1946*)). D. W. Woolley has shown also that a characteristic alopecia in mice can be prevented or cured by inositol (*Nutrition Reviews* **2,** *163* (*1944*); **3,** *88* (*1945*)). Other deficiency signs which, however, have not always been confirmed by subsequent investigators are alopecia, including "spectacled eyes," and failure of lactation in rats, failure of growth in guinea pigs, rats, and hamsters, a characteristic reproductive disorder of hamsters, and encephalomalacia and exudative diathesis in chicks (*Ibid.* **1,** *197* (*1943*); **2,** *163* (*1944*); **3,** *88* (*1945*)).

The function of inositol in the animal body is not known but it is perhaps significant, particularly in the light of its lipotropic activity, that it is a constituent of certain phospholipids (*Nutrition Reviews* **3,** *88* (*1945*)). An unconfirmed report has appeared which suggests that inositol may form a complex in the animal body with alpha-tocopherol (vitamin E) (*Ibid.* **3,** *259* (*1945*)).

Para-aminobenzoic acid is a growth factor for certain microorganisms and a potent antagonist of sulfonamide drugs (*Nutrition Reviews* **1,** *155* (*1943*)) but there is considerable difference of opinion among investigators as to whether it is a dietary essential for animals. The report of its curative effect in human achromotrichia has been effectively controverted and attempts to confirm that it has a similar effect in rats have failed (*Ibid.* **1,** *365* (*1943*)). Conflicting data concerning the effect of para-aminobenzoic acid on growth and lactation in rats have been presented (*Ibid.* **1,** *197* (*1943*); **2,** *163* (*1944*)). An unconfirmed report has appeared that this factor, together with ascorbic acid will, under certain conditions, promote growth in chicks (*Ibid.* **2,** *217* (*1944*)). Encouraging results have been obtained in the treatment of rickettsial diseases with para-aminobenzoic acid but the bearing which this finding has on the position of this compound in nutrition is not known (*Ibid.* **4,** *87* (*1946*)).

TREATMENT OF INFECTIOUS HEPATITIS BY DIET AND REST

Although recent interest in the effect of proper nutrition on normal hepatic function has centered chiefly upon the clinical aspects of chronic disorders such as cirrhosis, it is logical to inquire into a possible role that diet might also play in such acute diseases of the liver as infectious hepatitis. The problem may be attacked in two ways: (1) the previous and current diets of persons acquiring infectious hepatitis may be examined to see whether they are in any way inferior to those of similarly exposed persons who escape it, or (2) an improved diet and special supplement of protein, amino acids, and vitamins may be given patients with infectious hepatitis to see whether they reduce mortality, bring about recovery, or speed convalescence when compared with a control group. The extensive experience with epidemics of infectious hepatitis gained during the recent campaigns in North Africa, Sicily, and Italy by British and American medical officers, now being published, is helping to clarify this problem even if it does not supply the final answer.

An investigation of the diet was undertaken as part of a comprehensive study of acute infectious hepatitis reported by A. M. McFarlan (*Quart. J. Med.* **14,** (*N.S.*) *125* (*1945*)). The evidence he was able to gather indicated that dietary factors did not play any measurable part in susceptibility to the disease, the morbidity from which was explained wholly on the estab-

lished principles of infections. Although further study, where it is possible to obtain more precise data regarding the quantitative aspects of nutrition in infectious hepatitis, may indicate some influence, it appears that it will be of minor importance.

A second study, an evaluation of diet as a therapeutic measure, was undertaken by J. D. Hughes (*Bull. U. S. Army Med. Dept.* **4,** *662 (1945)*) on a rather limited number of patients with acute primary infectious hepatitis. Twenty-six cases (group A) were treated by strict bed rest and a diet consisting of about the following: protein 180 to 200 g., carbohydrate 500 to 600 g., and fat 50 g. per day. Nineteen cases (group B) were used as controls and were allowed full activity and free choice of food at the ambulatory patients' mess. Both groups of patients had clinical jaundice but had never had a previous attack of jaundice and no major illness or injury within six months. They were observed simultaneously. Every week the icterus index, blood phosphatase, cephalin-cholesterol flocculation test, and sedimentation rate were measured on all patients. Accurate weight records were kept. Size of the liver and degree of tenderness were noted frequently. An exercise tolerance test was used to determine fitness to return to duty. The chief flaws in the experimental setup beside the small numbers in each group were the inability to measure the quantity or appraise the type of food eaten by members of group B, and failure to keep exercise and rest similar in the two groups.

Group A spent an average of sixty-seven and five-tenths days in the hospital as compared with ninety-two and three-tenths days for group B; in the treated group the livers returned to normal size in thirty-eight days as compared with seventy-three days in the untreated group. All subjects in group A gained an average of 7.2 pounds. Of those in group B, 4 actually lost weight, 3 were unchanged, and the average gain for the group was 2.1 pounds. The icterus index returned to normal almost a week earlier in group A than in group B. There was no appreciable difference in the rate of return to normal of the blood phosphatase. The cephalin-cholesterol flocculation test returned to normal slightly more rapidly in the treated cases, but a much larger percentage (59) in group B still had an abnormal test upon discharge than in group A (28). Differences in the exercise tolerance test were not important.

While the number of subjects was small, all the observed differences were in favor of the treated and rested group. It was noted that 6 patients in group A did not have palpable livers while in only 2 cases of group B was the liver not felt, suggesting that group A as a whole had less severe attacks of hepatitis. Moreover, it is impossible to state whether rest or diet should have credit for such differences as were observed, as the author points out. Although the data do not fully justify the conclusions drawn they are sufficiently suggestive to warrant further study, and the investigation is an example of what observations can be made under the exigencies of military medicine in the field with its obvious limitations upon an ideal experimental plan.

THE EXCRETION OF IODINE

Not much information on the excretion of iodine has been available, although the importance of the skin as an organ of iodine excretion has been recognized. H. Spector, H. H. Mitchell, and T. S. Hamilton (*J. Biol. Chem.* **161,** *137 (1945)*) in the course of an extensive study of the effects of high environmental temperature of some minerals and vitamins and their metabolites have included observations on iodine. During

eight of the experimental weeks of this study in which the subjects were on an adequate diet, iodine was determined in the dermal excretions collected in eight hour periods in a controlled environment, and in the urine collected over twenty-four hour periods. For four of the eight weeks each subject received 2 mg. of potassium iodide daily. During four of the weekly periods iodine was also determined in the daily food and in the daily feces of each subject. The subjects were 5 young men who stayed for eight hours daily, five days a week, in an exposure chamber. In alternate weeks the atmosphere was maintained "comfortable" and "hot-moist."

The methods of collecting "dermal excretions" and "undiluted sweat" are described, and the method used for the determination of iodine was a new modification of earlier methods and is described in detail by H. Spector and T. S. Hamilton (*J. Biol. Chem.* **161,** *127 (1945)*). The net loss of weight during exposure was calculated for each period by weighing the subjects (to the nearest gram) at the beginning and end of the experiment, and taking net loss as equal to initial weight plus the weight of all ingests minus the final weight and the weight of all urine and feces. Under the comfortable conditions the net loss averaged 0.92 g. per hour, which was chiefly insensible perspiration; under the hot-moist conditions the average loss was 676 g. per hour.

In undiluted sweat from 3 subjects there was 0.54 to 1.22 micrograms of iodine per 100 ml., and after fourteen days of daily dosing with 2 mg. of potassium iodide the concentration rose to 2.62 to 4.17 micrograms. It was found that profuse sweating increases dermal loss of iodine at high intakes, but at low intakes (700 micrograms per day) no consistent effect was observed. The effect of the hot-moist environment upon the urinary excretion of iodine was variable, so that no evidence was obtained to indicate that an environment which will produce sweating will increase iodine requirements. It was found that at least 75 per cent of the iodine lost from the body was excreted in the urine, and that the supplementation of intake by potassium iodide doses led to the excretion of most of the additional iodine intake in the urine. The fecal iodine excretion was found to be greater under the hot-moist conditions at high but not at normal levels of intake.

This painstaking study thus confirms the earlier studies showing that skin does excrete iodine, but suggests that the importance of this route has been exaggerated. Under all conditions examined much more iodine was excreted by the kidneys than by the skin, although under hot-moist conditions the relative dermal excretion was increased to as much as 22 per cent. The fecal loss of iodine was always small, of the order of the amount lost through the skin.

FAILURE OF PYRIDOXINE THERAPY IN NAUSEA AND VOMITING OF PREGNANCY

Medical literature contains innumerable reports of alleged successful therapy of many varieties of conditions by a still more varied number of remedial agents. The true knowledge of and success in the management of human ailments is often in inverse proportion to the number of different methods which are proposed for their treatment. Unfortunately, although proponents of various therapeutic agents may ultimately lose their enthusiasm for the agent in question it is unusual for them to report their failure or to retract the previously published recommendation. In no field of therapy is this more true than in that which concerns the use of various vitamins in the treatment of human disorders.

A troublesome complaint encountered in

the first trimester of pregnancy is nausea and vomiting. Often this becomes very severe, resulting in the condition, hyperemesis gravidarum. The cause of this disorder is not well understood. Emotional and psychic factors undoubtedly play some part. Sedation and general dietary supervision together with encouragement and assurance usually result in relief of the symptoms. In any event the nausea and vomiting generally disappear at the end of the first trimester of pregnancy. In the rare instances in which hyperemesis gravidarum occurs, more intensive management with replacement of electrolytes is generally beneficial. Thus it must be clear that the evaluation of therapeutic agents in the management of this condition is fraught with dangers of misinterpretation.

Various investigators have attributed to pyridoxine a beneficial role in the treatment of nausea and vomiting in pregnancy. B. F. Hart, V. P. Sydenstricker, and R. Torpin (*Bull. Univ. Hosp., Augusta, Ga.* **3,** *11* (*1941*)) treated 16 mild cases of nausea and vomiting with a pill containing thiamine, riboflavin, nicotinamide, pyridoxine, and calcium pantothenate. Within two or three days after treatment had been instituted vomiting ceased and nausea was partially relieved. Recurrence was reported as taking place in one or two weeks in some instances after the tablet had been discontinued. R. S. Willis, A. T. Morris, and W. E. Massey (*Am. J. Obst. Gynec.* **44,** *265* (*1942*)) used thiamine chloride in 46 patients and pyridoxine in 37. They concluded that pyridoxine was more beneficial than thiamine although their data are not convincing in this respect. B. B. Weinstein, G. J. Mitchell, and G. F. Sustendal (*Ibid.* **46,** *283* (*1943*)), and B. B. Weinstein, Z. Wohl, G. J. Mitchell, and G. F. Sustendal (*Ibid.* **47,** *389* (*1944*)) used pyridoxine but also employed sedation and "adequate dietary supervision" at the same time. They considered this vitamin to be of value although they admitted that analysis on a far larger number of patients was needed before final conclusions could be reached. W. M. Silbernagel and O. P. Burt (*Ohio State Med. J.* **39,** *1113* (*1943*)) reported complete relief in 38 out of 40 patients by the use of intravenous pyridoxine hydrochloride in doses of 25 to 50 mg. These patients received no sedatives and their diets were not altered.

H. C. Hesseltine (*Am. J. Obst. Gynec.* **51,** *82* (*1946*)) has attempted a more critical study of the value of pyridoxine. He was able at the Chicago Lying-in Hospital to assemble only 16 cases and of these only 2 required hospitalization, but one being an example of hyperemesis gravidarum. Of Hesseltine's 16 cases, 11 were given pyridoxine, 100 mg. daily by mouth and 100 mg. intramuscularly twice weekly. Of these patients only 3 had good results, 3 had fair results, and 5 had poor results. Placebo therapy was used in 3 secondarily. One of these obtained good results on placebo therapy subsequently and another one had an excellent result with moderate sedation. The control group consisted of 5 patients who were initially placed on placebo therapy. The tablets were of the same size as the pyridoxine ones and were given in the same manner and number. Three of these 5 patients were completely relieved of their nausea and vomiting by the injection of sterile water intramuscularly and placebo tablets. Two had poor results and were later placed on pyridoxine. The one patient with hyperemesis gravidarum in the entire series was benefited only when electrolytes, body fluids, and other deficiencies were corrected in accordance with usual obstetrical practice. In this study particular efforts were made to have the patients make no change in dietary and other habits or routines.

All of the patients who failed to respond to the pyridoxine or placebo therapy were cured by appropriate sedation and dietary management. When good results or arrest of vomiting and relief of nausea took place

they did so usually within a few days in both the pyridoxine and the control group. No evidence was found that those patients who required sedation, dietary, or other therapy for cure, improved any more rapidly after the pyridoxine administration than those who did not receive this vitamin.

Hesseltine concludes that treatment with pyridoxine in the dosages and methods employed was of no more value in mild or moderate nausea and vomiting of pregnancy than scores of other methods. In fact, on a percentage basis, better results were obtained by the administration of sterile water hypodermically and placebo tablets than by the use of pyridoxine.

NUTRITION IN THE AGED

The new interest in geriatrics brings to attention how little is known concerning nutrition in the aged. In a recent discussion J. Meyer, H. Sorter, and H. Necheles (*Gastroenterology* **5**, *398* (*1945*)) point out that there is a drop in the average rate of basal metabolism as age advances, the decline being more rapid in the male than in the female sex; but, to quote E. F. Du Bois ("Basal Metabolism in Health and Disease," *Lea and Febiger, Philadelphia* (*1936*)) "there is a great deal of variation in old people, probably depending on the degree of senility."

In the aged the caloric intake may be greatly reduced as compared with that of persons of younger age. Little is known concerning the actual caloric need of the aged. There is much to be learned concerning the significance of excessive fat in relation to arteriosclerosis, the role of excess carbohydrates in relation to diabetes, or of protein to renal damage. It is well known that the skin in the aged loses its turgor but whether this is due to dehydration is not clearly established. If it is due to dehydration the role of regressive changes in endocrine glands in producing changes in the water and salt content of the tissues is also a matter for investigation.

Meyer and associates have studied the digestive secretions in the aged and have found that the resting as well as the stimulated secretion of the salivary glands is diminished considerably. Together with a greatly decreased volume there is a greatly decreased ptyalin content. However, they did not find the amylase of the pancreas to be decreased in quantity. The volume, acidity, and pepsin content of the gastric secretion have been found to be reduced considerably with advancing age. Whether, in aged persons, the normal or increased pancreatic secretion with its ample secretion of trypsin can compensate for the reduced secretion of pepsin is a matter to be determined. The one component of pancreatic secretion which these workers have found to be decreased in old people is the lipase concentration. In such persons these workers have also found the blood lipase to be diminished considerably and significantly. Not a great deal is known about absorption in the aged but the same workers have found that the rate of absorption of galactose given orally is diminished significantly in old persons. It is not known but it is probably a fair assumption that other processes of selective or even of ordinary absorption may be diminished in old persons.

It is apparent that much study is needed for a clear understanding of nutrition in the aged. From a practical standpoint and on the basis of present information it would seem wise to recommend that the diet for the aged approximate that of the normal adult and that the supply of minerals and of the B-complex be maintained at a satisfactory or increased level. The nutritive value of the diet should be enhanced by giving consideration to such factors as the

consistency of food, size of meals, frequency of feedings, and liquid content of the diets as well as the food tradition of the people concerned.

THE METABOLIC FATE OF d-AMINO ACIDS

A. A. Albanese and his co-workers are continuing their study of the utilization of d-amino acids by man. Earlier papers (*J. Biol. Chem.* **155,** *101* (*1944*); **158,** *101* (*1945*); *Bull. Johns Hopkins Hosp.* **75,** *175* (*1944*)) have dealt with tryptophane, cystine, and methionine. A. A. Albanese, V. Irby, and J. E. Frankston (*J. Biol. Chem.* **160,** *25* (*1945*)) have now investigated the behavior of d-arginine.

Experimental procedures were similar to those used in the earlier studies. The amount of arginine administered to each subject was 2.10 g. of the hydrochloride (0.01 mole). It was given in water two hours after breakfast and followed by water at hourly intervals to maintain a sufficient flow of urine. Urine was collected for a two hour period previous to the dose, and for hourly periods thereafter, for three to twenty-four hours. Analyses of samples were made for total and amino nitrogen, arginine, urea, creatine, and creatinine.

Five experiments were made upon 3 subjects, but the results obtained in only one experiment are presented in detail. Following the ingestion of l(+) arginine hydrochloride, the excretion of arginine itself was only slightly increased, but after dl-arginine hydrochloride there was a marked increase in the excretion of arginine, as measured by the method of A. A. Albanese and J. E. Frankston (*J. Biol. Chem.* **159,** *185* (*1945*)). This excretion reached its peak in about three hours but continued well above ordinary levels for ten hours.

In the ten or twelve hours following dosage with the dl-arginine an average of 120 mg. more arginine was excreted than when l(+) arginine was given. It was assumed that the extra arginine excreted was d(−) arginine. There was no significant difference in the excretion of the other nitrogenous substances that could be traced to the type of arginine fed.

In vitro experiments on arginase utilization were also made with two arginase preparations; one was derived from rat livers and the other from a human liver specimen obtained at autopsy. Solutions of dl- and of l(+) arginine were treated under similar conditions with the two arginase preparations, and the activity of the arginase preparations measured by determination of the amount of urea produced. It was found that the human liver arginase quantitatively degraded both d(−) and l(+) arginine to ornithine and urea, whereas the rat liver arginase degraded only the l(+) arginine. The rat liver behaved in the same way as was reported many years ago for calf liver by O. Riesser (*Z. f. physiol. Chem.* **49,** *210* (*1906*)).

A. A. Albanese, J. E. Frankston, and V. Irby (*J. Biol. Chem.* **160,** *31* (*1945*)) have investigated the fate of acetyl-d-tryptophane. A. A. Albanese and J. E. Frankston (*Ibid.* **155,** *101* (*1944*)) had previously observed that only a 50 per cent utilization of dl-tryptophane was made by man, compared with that of l(−) tryptophane, and that ingestion of d(+) tryptophane leads to the urinary excretion of an "aberrant" indole derivative. In the present report six experiments were performed, the authors following their established technic of giving 0.01 mole of the amino acid and collecting and analyzing urine samples at hourly intervals afterwards.

They observed only a normal amount of indican in the urine after the ingestion of acetyl-tryptophane. The proportion of acetyl-tryptophane excreted as tryptophane in the next few hours after ingestion was

considerably greater than the proportion of a dose of tryptophane itself so excreted. It was established that none of the acetyl-tryptophane passed into the urine unhydrolyzed. In 6 experiments an average of 210 ± 10 mg. of tryptophane was excreted following the ingestion of 0.01 mole of acetyl-l-tryptophane, but only 95 ± 5 mg. after the ingestion of a like quantity of acetyl-dl-tryptophane, suggesting that in the racemic mixture it is predominantly the l form of acetyl-tryptophane which gives rise to the tryptophane in the urine. The authors conclude that, with the exception of a 5 per cent urinary loss, all the acetyl-dl-tryptophane may be available to man.

Comparative results for the mouse, rat, and man, comprising the new data plus all previously available in the literature, are tabulated. The point is thus brought out, that l- but not d-tryptophane is available to man while the rat can utilize either stereoisomer; but on the other hand man can utilize both forms of acetyl-tryptophane while only acetyl-l-tryptophane is available for the rat.

It must be questioned whether these differences between the species would still be evident if the technic used for each species were the same. Albanese, Frankston, and Irby have used the technic of the "overwhelming dose" whereas the studies on rats have been made by feeding the amino acid as a very minor constituent of a diet eaten throughout the day.

Both in the experiments with arginine and with acetyl-tryptophane the evidence that one stereoisomer was better utilized than the other depended upon the excretion of a rather small fraction of the isomer claimed to be poorly utilized. If the dose had been of the size of the ordinary daily ingestion, it is possible that each isomer would have appeared to be utilized equally well. The authors' claim that it would be beneficial to convert dl-tryptophane into the acetyl derivative before incorporating it into protein digests intended for the alimentation of man, cannot be accepted until tests employing extended dosing time with small quantities of the amino acids have been made.

A. A. Albanese, J. E. Frankston, and V. Irby (*J. Biol. Chem.* **160,** *441 (1945)*) have also examined the utilization of d-histidine. This compound was studied by the same technic used for the other amino acids, the urinary excretion of histidine being followed after ingestion of 0.01 mole of either l- or dl-histidine as the monohydrochloride. When l-histidine was ingested, a barely significant rise in the excretion of histidine above the basal level was observed; but ingestion of the dl-histidine was followed by a large increase in the excretion of histidine during the subsequent nine hours. The histidine was recovered from the urines in 4 experiments and identified as the d form; from 81.5 to 97.2 per cent of the d-histidine ingested in the racemate were isolated. Where the recovery of a d-amino acid from the urine after dosing is as large as this, then the significance of excretion differences cannot be questioned. In comparing the result with d-histidine in man with previous reports for other species, the authors note that both forms have been reported equally well utilized by the mouse (J. R. Totter and C. P. Berg, *J. Biol. Chem.* **127,** *375 (1939)*) and the rat (G. J. Cox and C. P. Berg, *Ibid.* **107,** *497 (1934)*) on the basis of feeding experiments using growth as the criterion of response. On the other hand, using excretion after a dose as the criterion, it has been observed that d-histidine is poorly utilized by the guinea pig (S. Edlbacher, M. Simon, and M. Becker, *Naturwiss.* **28,** *411 (1940)*), the rabbit (E. Abderhalden, "Physiologisches Praktikum," *3rd edition, p. 134, Berlin (1922)*), and the dog (E. Abderhalden and S. Buadze, *Z. f. physiol. Chem.* **200,** *87 (1931)*).

The whole situation with regard to utilization of the two optical isomers is at present confused, both with regard to species differences and technics of attack on the problem.

MATERNAL NUTRITION AND FETAL DEVELOPMENT

Maternal nutrition may be studied in relation to any one of several possible effects such as its influence on maternal health, on prenatal deficiency disease, on the course of pregnancy and labor, on reproduction and lactation, on malformation in the offspring, or on the general physical well-being of the infants at birth and during the neonatal period. This last named approach has been adopted by a group of investigators in the Department of Child Hygiene at the Harvard School of Public Health. An early publication of this group has been reviewed in this journal (*Nutrition Reviews* **1,** *386* (*1943*)).

A statistically significant relationship was shown to exist between the maternal diet and the condition of the infant. Of 31 infants whose mothers' diets were "excellent" or "good," 13 or 42 per cent were rated as "superior" and 14 or 45 per cent as "good" while only one infant was in the "poorest" group. On the other hand, of 36 infants whose mothers' diets were "poor" to "very poor" only one was "superior" and one "good" while 24 or 67 per cent were rated as "poorest." In the 216 cases studied, every stillborn infant, all but one of those who died within the first few days of life, all premature infants, all of those "functionally immature," and a majority of those with marked congenital defects were born to mothers whose diets during pregnancy were very inadequate. A statistically significant but less marked relationship was also found to exist between prenatal diet and the course of pregnancy. No mother whose diet was "excellent" or "good," but almost 50 per cent of those whose diets were "poor" or "very poor" had preeclampsia. There was also a tendency for the mothers whose diets were "poor" or "very poor" to have more difficult types of labor and to have more major complications at delivery even though their infants were, on the average, smaller than the infants born to mothers whose diets were "good" or "excellent." Since the relationship between the prenatal diet and the course of pregnancy was less marked than that between the diet and the condition of the infant, the authors concluded that when nutrition during pregnancy is inadequate, the fetus suffers to a greater extent than the mother.

In a subsequent report, B. S. Burke, V. V. Harding, and H. C. Stuart (*J. Pediatrics* **23,** *506* (*1943*)) recorded their analysis of the influence of the amount of protein in the maternal diet on the physical characteristics of the offspring. Of the 216 women studied, only 10 per cent consumed diets during pregnancy which contained 85 g. daily of protein. Sixty-eight per cent of the diets contained less than 70 g. of protein and 38 per cent less than 55 g. A significant relationship was found to exist between the protein content of the mother's diet and the birth length and birth weight of the infants and their physical ratings. From a detailed analysis of their data, Burke *et al.* concluded that when the maternal diets during the latter part of pregnancy contained less than 75 g. of protein, the infants tended to be short and light in weight and were most likely to receive a low pediatric rating in other respects.

Some further analyses of the data have been presented by H. C. Stuart (*Federation Proceedings* **4,** *271* (*1945*)). It appears that the osseous development of an infant at birth depends to a considerable extent on the maternal diet. The measure used was the presence of osseous centers in the hand, knee, and foot as shown by x-ray photographs. From these films each infant was given a rating of "advanced," "average," or "retarded." Among the 21 full term infants whose mothers' diets were "poor" or "very poor," only one was considered to have "advanced" osseous development while 13 or 61.9 per cent were "retarded." Among

the 29 infants whose mothers' diets were "excellent" or "good," 8 or 27.6 per cent were rated as "advanced" and 3 or 10.4 per cent as "retarded." An even stronger relationship was shown between the osseous development of the child and the level of protein in the maternal diet while the correlation with the level of calcium was somewhat less striking.

In considering the question of why so many infants whose mothers' diets had been inadequate were in unsatisfactory condition at birth, Stuart analyzed the relationship between these findings and the health of the mother, particularly in regard to preeclampsia, nausea, vomiting, and anemia. There were 12 cases of preeclampsia in the fair diet group and 16 in the poor to very poor diet group. Twenty-three of the 28 infants born to those women failed to obtain a good rating. Of 16 cases of complication with severe nausea and vomiting 5 in the poor diet group and one in the fair diet group later had preeclampsia. The other 10 cases were fairly evenly distributed between the good, fair, and poor diet groups and what happened to the infant appeared to depend on the quality of the diet which the mother succeeded in taking rather than on the nausea and vomiting *per se*. Of 11 cases of severe anemia, one mother had a "good to excellent" diet, 6 had "fair," and 4 had "poor to very poor" diets. Of the 11 infants 5, constituting a very high percentage, showed unsatisfactory physical condition at birth.

In planning for the future, Stuart suggests that if we are to obtain a clear understanding of the influence on health of maternal dietary habits, we should study suitable samples of four groups: first, married women of childbearing age, second, pregnant women during the last trimester of pregnancy, third, newborn infants, and fourth, infants at about 3 months of age. In this way a more complete picture of maternal nutrition and its effect on both mother and offspring will be obtained.

The results obtained to date from these studies are striking and valuable. Confirmation by independent investigators, acceptance by obstetricians, and the results of the more complete studies now being planned will be awaited with interest.

A NUTRITION SURVEY OF SOME VERMONT CHILDREN

H. B. Pierce *et al.* (*New Engl. J. Med.* **233,** *612 (1945)*) have reported data bearing on the nutritional status of 386 schoolchildren in Vermont. These children were from eight different groups, some in institutions, some from rural areas, others from high or low economic urban areas. They ranged in age from 3 to 15 years. The method of selecting the particular group of subjects is not indicated, hence it is not possible to determine whether the data can be generalized as representative of children in the area. The study was made during September and October, 1944.

The technics for evaluation of nutriture included a one day qualitative diet history (obtained from 186 children); height-weight measurements of one third of the children; physical inspection for "a few specific signs related to the past or present nutritional status of the child" (381 subjects); and laboratory estimations of hemoglobin and plasma ascorbic acid levels (170 and 176 subjects respectively). No reason is given for the discrepancy in the number of subjects examined and the number of certain laboratory tests carried out. Thus, in one group (B) 90 children were examined while 63 had ascorbic acid determinations made. It seems possible that laboratory studies may have been reserved for the subjects who appeared most likely to be malnourished. If so, this would obviously bias the sample and hence prevent general-

ization of the laboratory data to the group as a whole.

The dietary data may be summarized as follows: 93 per cent of the subjects recorded the taking of milk on the day the diet record was kept; 90 per cent recorded meat and eggs on that day; 62 per cent recorded citrus fruits or tomatoes and 58 per cent recorded the eating of other fruits on the examination day. Vegetables, other than potatoes, were consumed by 55 per cent of the children on the day of examination.

None of the children exhibited "severe" grades of angular stomatitis or of scars at the corner of the mouth. The diagnosis of a severe degree of rickets, gingivitis, and folliculitis was in each instance made only once. On the other hand, the clinical diagnosis of "active or healed rickets of the chest, mild degree" was made one hundred and fifty-one times. Inasmuch as this diagnosis was not corroborated with x-ray studies or serum phosphatase levels it is difficult to be certain that these diagnoses are valid. The clinical diagnosis of mild active or healed rickets by a single inspection and palpation is likely to be a most unreliable procedure.

The listing of physical signs interpreted as evidences of malnutrition in this paper included "crusted eyelids" and "scars at corners of eyes." The basis of this interpretation is not given. The discussion implies that either vitamin A deficiency or riboflavin deficiency accounts for these findings. If this is correct, the evidence for the correlation should be presented inasmuch as it is not a generally recognized relationship. In a discussion of ocular signs the authors refer to the paper of V. P. Sydenstricker, W. H. Sebrell, H. M. Cleckley, and H. D. Kruse, (*J. Am. Med. Assn.* **114,** *2437 (1940)*) describing corneal vascularization due to riboflavin deficiency. A perusal of this paper reveals no mention of the lesions reported by Pierce *et al.* (*loc. cit.*). This tendency of many nutrition workers to list all minor variations, especially of the eyes, gums, and of skin and hair texture, as evidences of deficiency has been mentioned previously (*Nutrition Reviews* **3,** *251 (1945)*). If such findings are reliable indexes of nutritional status it is to be hoped that the authors will present evidences of the correlations supporting such a thesis since reliable specific signs of malnutrition are so urgently needed. On the other hand, until such evidence is available one must recognize the purely hypothetical interpretation of these signs.

The laboratory data do not indicate an alarmingly high incidence of deficiencies among these children. Eighty-four per cent of the subjects examined exhibited plasma ascorbic acid levels above 0.4 mg. per 100 ml. Only 7 per cent of the subjects had less than 0.2 mg. per cent. The hemoglobin levels of this group of children were remarkably high. The mean hemoglobin concentration appears to be about 15.2 g. per 100 ml. Ten per cent of the subjects were in the group with hemoglobin values from 16.5 to 17.9 g. The lowest 6 per cent of the determinations were in the range from 11.0 to 13.4 g. These levels may be compared with the hemoglobin observations on a group of subjects the "excellence of (whose) nutritive state was confirmed by careful medical examination, anthropometric measurements and detailed study of their bone development" and who "were as well standardized as is possible in human subjects, because they had been on a controlled, fixed dietary regimen for the preceding 8 months, during which time they had made excellent progress in growth and development." The hemoglobin levels of this latter group ranged from 11 to 13 g. (I. G. Macy, "Nutrition and Chemical Growth in Childhood," *Vol. II, pp. 1404 and 1406, Charles C. Thomas, Springfield, Ill. (1946)*). It appears, therefore, that the conclusion of Pierce *et al.* (*loc. cit.*) that "approximately 6 per cent of the children had levels indicative of a mild anemia" may be too arbitrary

a conclusion. Such attempts to set arbitrarily "normal" levels of hemoglobin must be carefully considered (*Nutrition Reviews* **3,** *202* (*1945*)).

The critical reader of this report will recognize that it is improbable that the samples should be considered representative of the children of the state as a whole, that the groups are too small for adequate statistical evaluation, and that the authors have not interpreted their findings in a conservative manner.

EFFECT OF N-METHYLNICOTINAMIDE CHLORIDE IN MAN

The identification of the fluorescent substance, F_2, of V. A. Najjar and L. E. Holt (*Science* **93,** *20* (*1941*)) with N-methylnicotinamide chloride (V. A. Najjar, D. B. McN. Scott, and L. E. Holt, *Ibid.* **97,** *537* (*1943*)) has made it important to determine whether this substance has antipellagra activity in man. It will be recalled that F_2 is found in the urine of normal individuals, and little or none is present in the urine of patients suffering from pellagra. One group of workers (V. A. Najjar *et al.*, *Bull. Johns Hopkins Hosp.* **74,** *406* (*1944*)) found methylnicotinamide chloride to have antiblacktongue activity in dogs, although L. J. Teply, W. A. Krehl, and C. A. Elvehjem (*Proc. Soc. Exp. Biol. Med.* **58,** *169* (*1945*)) could demonstrate little, if any, biologic activity.

G. A. Vance (*Bull. Johns Hopkins Hosp.* **77,** *393* (*1945*)) reports on the effects of administration of N-methylnicotinamide chloride to a typical case of pellagra. Four hour urine specimens showed an absence of F_2, and following administration of 20 mg. of nicotinamide intravenously, only a small and definitely subnormal output of F_2 in the urine was observed. This dose of nicotinamide produced no change in the color of the tongue of the patient and did not affect the dermatitis. Thereupon, 150 mg. of N-methylnicotinamide chloride were administered daily.

In the next five days the dermatitis improved markedly. The normal color of the tongue began to reappear as did the papillae. At the same time, however, the patient became hallucinated and wandered aimlessly about the halls of the ward. When 50 mg. of thiamine chloride and 20 mg. of riboflavin were given per day these psychomotor abnormalities disappeared after three days.

At the height of the patient's illness the electrocardiogram revealed low amplitude in the deflections produced by the cardiac impulse and changes in the T waves were also noted. Following administration of N-methylnicotinamide chloride a marked increase in the amplitude of the QRS deflection was observed and the abnormalities in the T waves disappeared. This observation is of interest because others, for example H. Feil (*Am. Heart J.* **11,** *173* (*1936*)), have described electrocardiographic abnormalities in pellagrins. These changes have been attributed to thiamine deficiency, but in the case described by Vance, improvement was observed before thiamine was administered. Unfortunately the illustrations which are published do not show the standardization of the electrocardiograms. Presumably the standardization was the same each time they were made, but it should be noted that the changes in the electrocardiograms which Vance credits to the therapy, could be attributed to technical variations.

It is strange that, although the dermatitis and glossitis disappeared during the administration of N-methylnicotinamide chloride, the psychomotor manifestations became more marked under these circumstances, for nicotinic acid is known to alleviate the psychic manifestations of pellagra. While

the reported results, therefore, are of interest there are a sufficient number of inconsistencies in regard to the possible biologic effectiveness of N-methylnicotinamide to cause one to withhold conclusions until further evidence is produced.

METABOLISM OF PHENYLALANINE BY THIAMINE DEFICIENT RATS

It has been shown conclusively that phenylalanine and tyrosine are incompletely metabolized by scorbutic guinea pigs and by premature infants. Some years ago K. Closs and A. Fölling (*Z. f. physiol. Chem.* **254,** *258* (*1938*)) reported that phenylpyruvic acid appeared in the urine of thiamine deficient rats when extra phenylalanine was fed. This question has been reexamined by M. M. Kaser and W. J. Darby (*J. Biol. Chem.* **161,** *279* (*1945*)), who found the earlier evidence inconclusive; they point out however that a review of the pertinent evidence suggests the possibility that thiamine deficiency could lead to a secondary ascorbic acid deficiency in the dog and the rat and so explain the results reported by K. Closs and A. Fölling.

Both male and female albino rats were maintained on a simplified diet based on casein, sucrose, and cottonseed oil. This diet was supplied with other vitamins, but no thiamine was added; a control diet containing 2.5 mg. of thiamine per kilogram of diet was also used. The rats were started at 4 weeks of age and fed the control diet for three weeks, the thiamine free diet for five weeks, then the control diet for five weeks, and finally the thiamine free diet for eight weeks. They all developed signs of deficiency while on the thiamine free diet (2 rats died during the period of deficiency) but did well on the control diet. During each experimental period several twenty-four hour urine specimens were collected in bottles containing 1 ml. of glacial acetic acid, and kept at −20° C. until the analyses could be performed (one to five days). At intervals 100 mg. or 200 mg. of dl-phenylalanine dissolved in water with an equivalent of sodium carbonate were given by stomach tube at the beginning of the twenty-four hours during which urine was collected.

The urines were analyzed for hydroxyphenyl compounds before and after shaking with ether in the cold to extract phenylpyruvic acid. The nonextractable hydroxyphenyl compounds were not identified, and all hydroxyphenyl compounds were expressed as tyrosine equivalents. It was found that more hydroxyphenyl compounds were excreted by the rats when on the control diet than when on the thiamine free diet, and also that the excretion of hydroxyphenyl compounds following a dose of dl-phenylalanine was greater when they were on the control diet. The ferric chloride test for phenylpyruvic acid and homogentisic acid was however positive in only one (deficient) rat. It was realized that these results might reflect the difference in the age of the rats during the different experimental periods; or differences in the food intakes during the various periods, since casein has a high content of aromatic amino acids.

To test these possibilities the experiment was performed again with 6 pairs of pair-fed rats, one of each pair on the thiamine deficient and the other on the control diet, and using 200 mg. doses of phenylalanine. No significant difference was found between the excretion of hydroxyphenyl compounds by the two groups either before or after a dose of phenylalanine. With the larger doses of phenylalanine the urines of both deficient and control rats gave an intense green color, indicating the presence of pyruvic acid.

The data of K. Closs and A. Fölling (*loc. cit.*) had been obtained by means of qualitative tests on the urines of rats which were not pair-fed. It is clear therefore that there is no contradiction between their findings and those of M. M. Kaser and W. J. Darby (*loc. cit.*); and that there is no evidence that thiamine deficient rats are less able to metabolize dl-phenylalanine than normal rats.

TREATMENT OF LIVER CIRRHOSIS WITH CHOLINE AND CYSTINE

The treatment of hepatic disease on the basis of knowledge gained from experimental studies in which fatty, necrotic, and cirrhotic changes have been produced in the liver has been reported from a number of sources. Thus there are several clinical reports (G. O. Broun and R. O. Muether, *J. Am. Med. Assn.* **118,** *1403 (1942)*; W. H. Barker, *Med. Clin. North America* **29,** *273 (1945)*; L. J. Wade, *Ibid.* **29,** *479 (1945)*) in which choline in conjunction with a high protein, low fat diet, and vitamin supplements appeared to exert a favorable influence in the treatment of cirrhosis. A. H. Russakoff and H. Blumberg (*Ann. Int. Med.* **21,** *848 (1944)*) have reported similar favorable results and they refer to observations in 5 cases of alcoholic cirrhosis in which both choline and cystine were used. The use of choline and cystine in combination is based on the observations of P. György and H. Goldblatt (*J. Exp. Med.* **75,** *355 (1942)*) who found that choline is more effective when administered with cystine. These latter workers have pointed out that in the experimental studies in which choline alone has appeared to prevent hepatic injury the diets contained a certain amount of cystine.

A. J. Beams (*J. Am. Med. Assn.* **130,** *190 (1946)*) reports on the use of choline together with cystine in the treatment of 20 patients with cirrhosis of the liver and ascites. Twenty patients received from 1.5 to 3.0 g. of choline and the same amount of cystine daily, divided into three doses, for periods of one to five months. They were also given a high protein and low fat diet which consisted of approximately 110 g. of protein derived from meat, vegetables, and dairy products, 50 to 70 g. of fat, and 250 g. of carbohydrate supplemented with 30 to 45 g. of brewers' yeast daily. Of these patients, 12 had no enlargement of the liver whereas 8 had definitely enlarged livers. In addition to these 20 cases, a control group of 15 patients with large livers and ascites was observed. These received the same diet and medication except for the choline and cystine. The three groups of patients were much alike in respect to age, duration of the disease before treatment, the incidence of alcoholism, the incidence of jaundice, and the evidences of advanced hepatic failure.

A striking difference was noted in the response of patients with large livers as compared with those with no liver enlargement. In the former, excretion of fluid (diuresis) began about two weeks after the medication was started. At first, the diuretic effect was very slight but it gradually increased until at the end of a month a negative water balance existed. At the end of two months fluid could no longer be demonstrated in the abdomen and the livers were much smaller. The serum albumin showed a definite rise in most of these patients after a month of treatment, from an average of 2.47 g. per 100 ml. to 3.08 g. per 100 ml. At the end of three months the serum albumin ranged from 3.4 g. to 4.0 g. per 100 ml. in all of the patients except one in whom the level never exceeded 2.86 g. Even in this patient, however, the ascites disappeared and the liver became smaller. In contrast the cephalin-cholesterol flocculation test became negative in only 2 pa-

tients, one at the end of the month and another after a period of a year.

None of the patients showed any signs of a return of liver failure although one of them died of a ruptured dilated vein in the esophagus at the end of one and a half years. A second patient died of bronchial pneumonia after a similar lapse of time. The remaining patients were enjoying good health at the time of the report. Only one of the patients with no liver enlargement but treated with choline and cystine was alive at the end of a year. In contrast to the survival of the patients receiving choline and cystine, only 6 of the 15 control patients with enlarged livers who received no choline or cystine, were alive at the end of one year.

These observations are somewhat promising. It is well known that spontaneous remissions occur in cases of cirrhosis and that these are more likely to take place in persons with an enlargement of the liver. It may be argued that it is in those cases in which there is liver enlargement and, consequently, probable fatty changes, that one can hope for benefit with treatment or may expect spontaneous improvement. The latter may represent the effect of an unrecognized mechanism for correcting the abnormality. In persons with no hepatic enlargement and presumably comparatively little fatty change, not much benefit can be expected from treatment.

As to the wisdom of using choline and cystine in addition to a diet already high in protein and supplemented with yeast, Beams argues that appetite may be so poor that many patients with cirrhosis of the liver are unable to tolerate the large amounts of food they should take. Supplementing the diet with choline and cystine assures them of substances which may be required in the repair of the liver. It is to be noted that R. G. Fleming and A. M. Snell, who described the effects of high protein, high vitamin diets (*Am. J. Digest. Dis.* **9,** *115* (*1942*)), also observed that favorable results occurred in patients with large livers and they expressed the opinion that "cures" probably are to be expected among patients who possess various degrees of fatty metamorphosis and degeneration without extensive periportal fibrosis.

EFFECTS OF AMINO ACIDS ON BACTERIAL RESISTANCE TO PENICILLIN

The majority of gram-negative bacilli are described as highly resistant to penicillin. G. Shwartzman (*Science* **100,** *477* (*1944*); **101,** *276* (*1945*)) however, has found that the gram-negative bacillus Escherichia coli may be considerably more susceptible to the drug than has been assumed hitherto. This susceptibility can be demonstrated if appropriate concentrations of the organism are used. He has observed also (*J. Exp. Med.* **83,** *65* (*1946*)) that the resistance of the organism to penicillin varies with the concentration of certain substances in the culture medium. Organisms which grew abundantly in basal medium did not grow as well in this medium when it was mixed with blood serum, yeast extract, meat infusion broth, or a "vitamin-free" casein acid hydrolysate. It was observed that the materials just mentioned showed a distinct antagonism for penicillin which, compared on the basis of nitrogen concentration, was most marked with casein hydrolysate and yeast extract. In view of the significant antipenicillin potency of casein hydrolysate it was assumed that amino acids might be responsible for the effect. This assumption was strengthened by the finding that clearcut antagonism could be obtained with certain amino acids. Of these cystine was one of the most potent.

The antagonism exerted by the amino acids was characterized by lack of strict quantitative relationship between the

amount of substance used and the effect obtained. The antagonism remained approximately the same within a wide range of decreasing concentrations. There was no correlation between the effect of amino acids upon bacterial population at the expiration of the incubation period and their penicillin-antagonizing and penicillin-enhancing potencies. Prepassages in mediums of various concentrations of antagonistic amino acids altered the resistance of E. coli to penicillin.

Shwartzman observed that the antipenicillin activity of the amino acids could be reversed significantly by dl-methionine. Upon addition of methionine, methionine sulfoxide, and threonine a marked enhancement of penicillin susceptibility of broth cultures of several organisms was observed. The enhancement was apparently due to the ability of this amino acid mixture to reverse effectively the action of the antagonists present in the cultures. Of these three substances, methionine seemed to be essential for the enhancement of penicillin susceptibility, and threonine and methionine sulfoxide facilitated the effect of methionine.

Shwartzman concludes that the most likely explanation for this interesting phenomenon is that the antagonism is due to the effect of amino acids upon bacterial metabolism rather than being caused by their interaction with penicillin itself. He points out that various investigators have shown that microorganisms may acquire the ability to synthesize certain vitamins and amino acids essential to growth when trained to grow in their absence. Conversely a loss in synthetic function may be incurred by continued growth of an organism in an evironment in which the essential metabolite is present and, therefore, no need arises for its synthesis. Thus, it may be that a substrain of an organism grown serially in the presence of casein hydrolysate may lose its ability to produce the factors antagonistic to penicillin, inasmuch as the medium contains a significant concentration of antagonistic amino acids. On the other hand, when a substrain is trained to grow on a medium of meat infusion agar containing a lower concentration of antagonistic amino acids than the casein hydrolysate, the ability of the organism to produce antipenicillin factors may be proportionately restored, making the substrain more resistant to penicillin than the first one. Finally, when continually grown in basal medium devoid of antagonistic amino acids the ability of the organism to produce the antipenicillin factors may become still more pronounced, the resulting penicillin resistance being the highest. It is suggested that the —S—S linkage may be related to antipenicillin potency. The $CH_3 \cdot S$ grouping may be associated with the enhancement of penicillin activity.

These interesting observations will surely lead to a better understanding of the mode of action of penicillin as well as of bacterial metabolism. What significance they may have in regard to the broader question of the relationship of the nutritional state to resistance to infection can only be surmised at the present time.

PROTEIN INTAKE AND NIACIN METABOLISM

M. M. Wintrobe, H. J. Stein, R. H. Follis, and S. Humphreys (*J. Nutrition* **30,** *395* (*1945*)) have reported a relation between the protein content of niacin deficient diets and the deficiency signs which resulted when these diets were fed to young growing pigs. The standard basal diet used by these workers consisted of: 26.1 per cent crude casein, 11.0 per cent lard, 57.7 per cent sucrose, and 5.2 per cent salt mixture. When young pigs were fed this diet adequately supplemented

with thiamine, riboflavin, pyridoxine, choline, and pantothenic acid, but not with niacin, there were no deficiency signs except slightly subnormal growth in certain cases. However, when the protein content of this basal diet was reduced to 10 per cent and the lard increased to make up for the casein reduction, the omission of niacin resulted in markedly impaired growth, rough coats, diarrhea, poor appetite, and severe anemia. When pigs were fed this low protein diet plus a niacin supplement, they appeared to be much better nourished, although their rate of growth was not as great as that of the pigs which received the high protein diet without any added niacin. In an effort to determine whether enough niacin had been present in the 26.1 per cent crude casein of the high protein diet to prevent the development of a frank niacin deficiency, the crude casein in the diet for one group of pigs was completely replaced by vitamin free casein. No deficiency signs were observed in these pigs despite the lower niacin content of this high protein diet. Hence the niacin present in the higher crude casein level was not responsible for the prevention of deficiency symptoms. Since the fat content of the low protein diet was higher than that of the high protein diet, a small group of pigs was maintained on a low protein diet which had the same fat content as the high protein diet. No change in the production of the deficiency signs occurred with the reduced fat content.

Measurements of the urinary niacin, nicotinuric acid, trigonelline, and related compounds were made as a means of determining the degree of niacin deficiency. An extremely wide variation in the excretion of these metabolites was observed. The pigs which were fed a low protein diet without a supplement of niacin were the only ones which showed a marked and consistent reduction in the amounts of the niacin derivatives which were excreted.

An interrelation between the quality of the proteins in corn and niacin deficiency has been discussed previously (*Nutrition Reviews* **3,** *267* (*1945*)). W. A. Krehl, L. J. Teply, and C. A. Elvehjem (*Science* **101,** *283* (*1945*)) observed that the growth of white rats was greatly reduced when two parts by weight of corn meal or corn grits were added to three parts of a simplified, low protein diet. When 100 g. of this diet were supplemented with 1.0 mg. of niacin, the rate of growth in rats fed this diet was similar to that of the rats which were fed only the simplified, low protein diet but without added corn. Similarly, when the casein content of the basal diet was increased from 15 to 20 per cent, no growth inhibition was produced by the addition of corn meal or corn grits. In an investigation of the mechanism through which the increase in the protein content of the diet counteracted the growth depression produced by corn, W. A. Krehl, L. J. Teply, P. S. Sarma, and C. A. Elvehjem (*Ibid.* **101,** *489* (*1945*)) found that the addition of 0.05 per cent of 1(-)tryptophane prevented the inhibitory effect of corn.

The relation between various other dietary components and the interplay between niacin and tryptophane in the white rat have been investigated by W. A. Krehl, P. S. Sarma, L. J. Teply, and C. A. Elvehjem (*J. Nutrition* **31,** *85* (*1946*)). In order to test the effect upon growth of cereals other than corn, polished rice, whole wheat flour, refined wheat flour, whole rye flour, whole rolled oats, and soybean flour were incorporated individually into the purified diet in the same manner as for corn and corn grits. In every case good growth resulted even though some of these cereals had a lower niacin content than the corn products. The higher tryptophane content of these cereals may have been responsible, at least partially, for the normal growth observed. These workers also found that the type of carbohydrate in the purified diet to which the corn grits were added, exerted an effect on the growth depressing action of the corn grits. When the sucrose

of the diet was completely replaced by glucose or dextrin or partially replaced by lactose, this growth depressing action was greatly reduced. When the vitamin levels of the basal and of the corn supplemented diets were lowered to 60 per cent of the original level, the rate of growth of those rats fed the basal ration was reduced; in addition the effect of glucose in protecting against the growth depressing action of corn grits was lost. However, the increase of the vitamin levels to three times the original concentrations did not produce any significant effect on the growth rates.

Since corn appears to owe its growth depressing effect to its low tryptophane content, Krehl *et al.* studied the relation of tryptophane deficient diets which did not contain corn to the niacin requirement. A combination of wheat gluten and gelatin was used as a source of protein, a source which was reasonably complete in all known essential amino acids except tryptophane. When sucrose was used as the carbohydrate in this tryptophane and niacin deficient ration, growth was very poor. The addition of adequate amounts of either tryptophane or niacin to this diet resulted in normal growth. Again both glucose and dextrin exhibited such a strong protective effect against the deficiencies present that the addition of either tryptophane or niacin did not significantly increase the rate of growth. These data indicated even more strongly the interrelation between the requirements of the rat for tryptophane and niacin, and showed definitely that this interplay could be independent of corn.

The observations of Krehl and co-workers probably represent the earliest production of a niacin deficiency in the white rat. This was possible through the addition of corn to a purified diet or through the use of a diet which was itself deficient in tryptophane as well as niacin. In both cases the addition of either tryptophane or niacin resulted in an increased growth rate. W. A. Krehl, L. J. Teply, and C. A. Elvehjem (*Proc. Soc. Exp. Biol. Med.* **58,** *334 (1945)*) have observed a threefold increase in the niacin requirement of the dog when fed a purified diet in which 60 per cent of the sucrose had been replaced by unenriched corn grits. In the pig, niacin deficiency signs have been described previously by several workers. In each of the swine studies, the diets have been deficient not only in niacin but were borderline or deficient in numerous other essential nutrients. The relation between protein level of the diet and the niacin requirement described by Wintrobe and co-workers is undoubtedly closely related to the interrelation between tryptophane and niacin deficiencies described by Krehl *et al.*

These studies on the relation of both the quality and the quantity of protein in the diet to niacin metabolism represent an early stage in a newer phase of nutritional research. In any new field of experimental science, there has always been an imperative need for the simplification of all procedures in order that there might be developed a standardized regimen with only one variable. Early investigations of dietary requirements made necessary the development of highly purified, simplified rations in which many individual nutrients could be provided in adequate amounts while the one under investigation was altered at will. With this implement it has been possible to isolate and characterize many of the essential nutritional factors and to determine the requirements of various animal species for each of these nutrients when the animals were maintained on this otherwise adequate, standardized regimen. However, as the science of nutrition progresses, it has become increasingly more important to study the interrelation between two or more essential nutrients. In many cases, the use of natural foodstuffs in experimental diets has stimulated this change in emphasis. The ultimate object to be desired in such a progression would be the determination of the human requirement for each essential nutrient under any dietary pattern and the method by which this requirement could be satisfied most efficiently.

PYRIDOXINE IN RELATION TO POIKILOCYTOSIS IN DAIRY CATTLE

A high incidence of poikilocytosis in certain dairy cattle in Michigan has been observed by J. T. Reid, C. F. Huffman, and C. W. Duncan (*Arch. Path.* **39,** *351* (*1945*)). Four hundred and twenty-three animals ranging from young calves to mature cows were used in the study of the occurrence and signs of poikilocytosis; 233 of these cattle were found to be affected with this syndrome of abnormally shaped red blood corpuscles. In 14 cases more than 91 per cent of the erythrocytes were observed to be poikilocytic. Anorexia, thinness, unthriftiness, a dry and harsh condition of the hair coat, and in growing animals, a severely retarded rate of growth were the signs which were observed to accompany a poikilocyte count of over 50 per cent of the red blood corpuscles. A depraved appetite was frequently observed. However, poikilocytosis appeared to be independent of the number and volume of the red blood cells, hemoglobin, plasma calcium, inorganic phosphorus, and magnesium content.

Since the incidence of poikilocytosis varied in neighboring herds of cattle and could be readily produced experimentally in young cattle by feeding semirestricted rations, these authors (*J. Nutrition* **30,** *413* (*1945*)) were able to investigate the relationship of antianemic mineral mixtures, yeast, pyridoxine, riboflavin, and nicotinic acid to the incidence of this blood disorder. When young calves were fed a diet consisting solely of whole milk and a cereal breakfast food (rice krispies), most of them developed a severe poikilocytic condition which was frequently complicated by a severe anemia. In a few cases there was a severe anemia without poikilocytosis. When a mineral mixture containing 250 mg. of iron, 250 mg. of manganese, and 25 mg. of copper was fed daily to each of 7 affected calves, there was a gradual increase in the hemoglobin concentration without any change in the severity of poikilocytosis. A similar result was observed when the same supplement plus 5 mg. of cobalt was fed daily to each of 20 affected calves. When a supplement of 200 g. of dry brewers' yeast or 100 g. of live yeast were fed daily to affected calves, the distortion of the red blood cells was decreased markedly without a change in the hemoglobin concentration. An increased growth rate accompanied the disappearance of the abnormal red blood cells. Similarly when a supplement of 5 to 20 mg. of pyridoxine was given daily, there was a decrease in the number of poikilocytes but the period of recovery was much slower. When a supplement of 40 mg. of pyridoxine was given daily, there was a complete absence of poikilocytes within three to four weeks after therapy was begun. In all cases the disappearance of poikilocytosis was accompanied by an improvement in the general health of the animals and an accelerated growth rate. It was found that supplements of 25 mg. of riboflavin or 50 mg. of nicotinic acid per day for as long as seventy days were completely ineffective in the treatment of this condition.

Four cows with rumen fistula, all with open or unplugged fistulas, were found to have an incidence of 15 to 99 per cent poikilocytes. When brewers' yeast was fed, there was a decrease in the amounts of poikilocytes in the blood. When the supplement of yeast in these mature animals was discontinued, there was a recurrence of the poikilocytic condition.

The synthesis of pyridoxine in the rumen of the cow has been demonstrated by various workers (L. W. McElroy and H. Goss, *J. Nutrition* **20,** *541* (*1940*); M. I. Wegner, A. N. Booth, C. A. Elvehjem, and E. B. Hart, *Proc. Soc. Exp. Biol. Med.* **45,** *769* (*1940*); **47,** *90* (*1941*)). However in the young calves and in the cows with open rumen fistulas described by Reid and co-workers, there was apparently an inadequate amount of pyridoxine in the diet of these animals

and an inability to synthesize pyridoxine. Growth and hematopoiesis were normal only when adequate amounts of pyridoxine were supplied as a supplement to the restricted diet.

It is unknown at present whether pyridoxine has any relation to poikilocytosis (sickle cell anemia) in man. R. W. Vilter, H. S. Schiro, and T. D. Spies (*Nature* **145,** *388 (1940)*) injected 50 to 100 mg. of pyridoxine intravenously each day for ten days into 3 pellagrins with a macrocytic anemia and into 2 patients with pernicious anemia. A subjective feeling of increase in strength and well-being was observed along with an increase in the reticulocyte count. It was not inferred that pyridoxine was an antipernicious anemia factor. The observations of Reid and co-workers further emphasize this point since the response to yeast or pyridoxine administration in poikilocytic dairy cattle was the production and maintenance of normal erythrocytes without an increase in the hemoglobin concentration.

CHEMOTHERAPY THROUGH COMPETITIVE INHIBITION

Important as was the discovery of the therapeutic value of the sulfonamides, of even greater importance was the explanation, or at least partial explanation, of their mode of action. As a result, there has been introduced into the search for chemotherapeutic agents a much needed rationale, a rationale that has deep biologic implications not only for pharmacotherapy, but also for other aspects of pharmacology and even endocrinology.

A. D. Welch (*Physiol. Rev.* **25,** *687 (1945)*) has reviewed in a stimulating manner the investigations of the mode of action of the sulfonamides and the work along other lines that has already resulted from these basic studies. It now seems to be clearly established that sulfonamide and its various derivatives exert their action on microorganisms by interfering with the use of an essential metabolite, para-aminobenzoic acid (PAB). The important point about this interference is that it appears to result from a competition with PAB for a point of combination with some other essential cellular compound (or compounds). This competition obeys the mass law. That is, the degree of inhibition is determined by the ratio of sulfonamide to PAB concentrations to which the microorganism is exposed. Thus an increase in PAB concentration will allow bacteria to flourish in the presence of an amount of sulfonamide which would otherwise have "starved" them. This ability of the essential metabolite to overcome, when present in excess, the harmful effects of a drug is usually regarded as proof of "competitive inhibition," particularly if the reversal of action obeys the mass law. Competitive inhibitors in general have a structure which is similar enough to that of the metabolite to allow it to combine with the same cellular compound but which differ sufficiently so that the resultant complex cannot perform its biologic function.

As a result of the findings with the sulfonamides, it was immediately evident that drugs might be found to compete with other metabolites essential to the disease producing organism, and that it might be possible to find as many series of chemotherapeutic agents as there are essential metabolites. This hope has already been strengthened by the discovery of a variety of drugs which compete successfully with a great many compounds required by living cells. It is therefore somewhat disappointing to learn that, in spite of intensive efforts, not one of these competitive inhibitors has yet proved satisfactory as a chemotherapeutic agent. It is evident that a simple competition with an essential metabolite does not suffice to confer therapeutic value on a drug. Hence it would be useful to follow

Welch's discussion of the requirements that must be met before a competitive type of drug can achieve success.

(1) The drug must do more harm to the invader than to the host. This means that it must either interfere with a metabolite of more importance to the invader than to the host, or else the drug must be able to compete with the metabolite more satisfactorily in the microorganism than in the infected animal. Furthermore, the drug itself must not be for other reasons too toxic. (2) In general, the concentration of drug required to affect inhibition should not be too great. The ratio of drug to metabolite necessary for inhibitory effects (the so-called antibacterial index) varies enormously with different agents. (3) The essential metabolite which is being interfered with should be one that is required in very small amounts. Obviously if a particular metabolite were required in 1 per cent concentration by the infected animal and the antibacterial index of a competitive inhibitor were 200, it would be impossible to give sufficient drug to be effective. (4) The drug must not be excreted or destroyed too rapidly, otherwise therapy would be difficult. However, excretion and distribution can usually be readily altered by appropriate changes in the drug molecule. (5) The drug must penetrate the bacterial cell. (6) The concentration of the metabolite must not be too high in the body fluids of the host, otherwise inordinate amounts of drug would be required to produce inhibition.

Aside from the sulfonamides, none of the competitive inhibitors has as yet met the above requirements. There follows a rather imposing list of metabolites for which inhibitors have been found with a suggested explanation in parenthesis for failure of their respective inhibitors to be useful therapeutic agents: Tryptophane, methionine, phenylalanine (the metabolite is required in too high a concentration by the host); pyridoxine (probably too essential for the host, but it has been suggested that quinine and atabrine act on the malarial organism by competition with pyridoxine); pantothenic acid (the concentration of the vitamin in the body fluids is too great, the antibacterial indexes are too large, and drugs used thus far are excreted too rapidly); thiamine (the inhibitor apparently causes more damage to the host than to the microorganism); adenine and guanine (reasons for failure are not clear, presumably concentrations of these compounds in body fluids are too large to overcome); riboflavin and biotin (although inhibitors of these compounds have not yet proved to be successful chemotherapeutic agents, they appear to be promising and deserve further investigation). It is of interest that inhibitors for both ascorbic acid and vitamin K have been described, although presumably they could be of no value as bacterial antagonists.

This raises the question of even wider usefulness of competitive inhibitors for the study of biologic processes and perhaps for the alteration of the action of hormones or other active endogenous compounds such as acetylcholine, adrenalin, and histamine. Since the search for the many possible compounds suggested by the analysis of the mode of sulfanilamide action has only commenced, it is to be hoped that present disappointment over the failure to find other chemotherapeutic agents will not discourage further intensive investigation.

THE ANTIFATTY LIVER FACTOR OF PANCREAS

The experiments of I. L. Chaikoff, C. Entenman, and M. L. Montgomery (*J. Biol. Chem.* **160**, *387*, *489* (*1945*)) have helped to clarify the mechanism of action of the antifatty liver factor of the pancreas. The fatty liver was known to follow the loss

of the external secretion of the pancreas: it appeared in dogs following ligation of the pancreatic duct, and in depancreatized dogs maintained with insulin. In both conditions the fatty liver could be prevented by feeding pancreatic juice. The authors had shown previously (*Ibid.* **138,** *477* (*1941*); **155,** *573* (*1944*)) that such fatty livers developed even though the dogs were fed a diet containing considerable choline and methyl groups, but they could be prevented by adding more free choline, or certain fractions of pancreas, to the diet. It was established that the effect of the pancreas fractions was not due to their choline content, since one of the fractions was devoid of choline, whereas the minimum effective dose of choline was as large as 35 mg. per kilogram of weight per day.

Over a decade ago I. L. Chaikoff and A. Kaplan (*J. Biol. Chem.* **106,** *267* (*1934*)) had reported that the fatty liver of depancreatized dogs maintained with insulin is accompanied by a decreased level of phospholipid in the blood. S. H. Rubin and E. P. Ralli (*Am. J. Physiol.* **129,** *578* (*1940*)) later noted the same change in the plasma of dogs after ligation of the pancreatic duct.

More recently it has been established that the phospholipids of plasma are predominantly choline-containing, and C. Entenman and I. L. Chaikoff (*J. Biol. Chem.* **160,** *377* (*1945*)) have shown that nearly all the choline in plasma is bound as phospholipids, with less than 5 per cent in the free form. These findings have led to further investigation in the two papers first cited of the relation of the pancreatic antifatty liver factor to the plasma choline.

In the first experiments reported the plasma choline level was followed in dogs before pancreatectomy, and afterwards when they were maintained with insulin. In each of 5 dogs the plasma choline fell by at least one-third; but it is curious that for one dog the level fell to one third of the initial level twenty-nine weeks after pancreatectomy, and then increased to two-thirds after a further twenty-seven weeks. A similar fall was demonstrated in 5 other dogs within ten to twenty-two weeks after ligation of the pancreatic duct. By the daily feeding of 1 g. of a pancreas fraction, the fall in plasma choline of 3 dogs which were depancreatized and then maintained with insulin on a lean meat diet, was completely prevented; indeed the level increased somewhat in all 3. This fraction "AR" was previously described by C. Entenman and I. L. Chaikoff (*J. Biol. Chem.* **138,** *477* (*1941*)), and shown to prevent the development of fatty livers in depancreatized dogs. In another experiment it was shown that in depancreatized dogs with low plasma choline levels, the fraction AR given daily for three weeks greatly increased the plasma choline, which fell again after withdrawal of the supplement. A second pancreas fraction, "27 C," known to prevent fatty liver in depancreatized dogs when fed at a level of 50 mg. daily, was also found to be effective at the same dose in raising the plasma choline of such dogs.

Even when the depancreatized dogs were maintained with insulin on a casein-containing diet almost devoid of choline, 100 mg. of fraction 27 C daily for three weeks were sufficient to raise markedly the decreased choline levels in the plasma of 2 dogs. Thus it was established that the pancreas antifatty liver factor is highly active in choline metabolism, and the authors drew the conclusion that the plasma phospholipids are intimately connected with the physiologic activity of circulating choline.

The final experiments reported were concerned with the feeding of free methionine to depancreatized dogs maintained with insulin on the lean meat diet. The dogs received 500 g. of lean meat daily, which provided about 0.5 g. of choline and 3.0 g. of methionine. The earlier experiments with the unheated pancreas fraction 27 C showed that this amount of meat served to maintain

normal plasma-choline when supplemented by 100 mg. daily of the active fraction free from choline. Five dogs were depancreatized and fed pancreas for one week only. Following this, 3 of the dogs (weighing 7.5 to 9.7 kilograms) were fed 2.1 to 3.0 g. methionine daily for twenty weeks, while the other 2 were held as controls. The dogs were then killed for liver fat and phospholipid determinations; the controls had fatty livers and the other dogs had not. The phospholipid analyses did not reveal any differences between the methionine-fed dogs and the controls.

This experiment indicates that the dog deprived of its external pancreatic secretion is able to synthesize choline from free methionine. The next question of interest therefore is: Why can the dog not synthesize choline from the bound methionine of the meat diet? The authors advance the hypothesis that the active factor in pancreas or pancreatic juice which makes the bound methionine available for choline formation is a proteolytic enzyme necessary for the liberation of the methionine from the protein of the diet. Such a hypothesis appears to be a possibility.

NUTRITIVE VALUE OF FISH PROTEINS

Since the common foods which supply animal protein have become increasingly inadequate to meet the demand for proteins of high biologic value, there has been a need for the evaluation of the nutritional adequacy of proteins from other sources. Generally the biologic values of the proteins of vegetable origin are lower than those of animal origin. Since the supply of fish represents a much larger source of potential protein for human consumption than has been utilized, H. J. Deuel and co-workers (*J. Nutrition* **31**, *175* (*1946*)) have compared the nutritive value of some fish proteins with that of casein. For these studies the proteins were isolated from edible fish muscle in such a way as to remove the easily perishable components and the factors which make fish by-products unpalatable. The fish proteins were precipitated isoelectrically and then purified by organic solvent extraction. The resulting preparations were "without flavor." The biologic value of the mackerel, sardine, and tuna proteins were tested in rat growth experiments and that of mackerel proteins was also determined by recovery of rats from hypoproteinemia. In both cases vitamin-test casein was used for the standard of comparison.

In the growth experiments the nutritional values of tuna proteins and casein were compared at 9 and 12 per cent levels, mackerel proteins and casein at 12 and 21 per cent levels, and sardine proteins and casein at 15 per cent levels. In each comparison study, 6 Sprague-Dawley rats received the fish protein diet while 6 litter mates received the diet which contained the same level of casein. The rats were allowed to consume the compared diets ad libitum for periods varying from twenty-four to thirty-five days. In all comparisons it was found that the diets which contained fish proteins produced better growth than those diets which contained the corresponding levels of casein. The most striking difference in growth rate was observed in the groups which received mackerel proteins or casein at a 21 per cent level. Since casein at an 18 per cent level is generally believed to supply adequate protein to produce maximum growth, it would be expected that the group of rats on the 21 per cent casein would show the best growth of all the experimental groups. However, the diet containing 21 per cent mackerel proteins produced about a 35 per cent more rapid growth rate than the diet containing 21 per cent casein.

From the growth curves it can be calculated that during the experimental period of twenty-eight days, the rats on the 21 per cent casein diet gained an average of 18 g. per week. This is not the maximum growth rate that can be obtained on a completely adequate, purified ration in which casein is the source of protein. The average rate of growth of the rats on the 21 per cent mackerel protein diet was about 25 g. per week. This value more nearly represents the optimum growth rate to be expected on an adequate purified diet when the sexes are equally represented. The questions might be raised as to whether the diet was inadequate in some one or more essential nutrients, and whether the fish proteins were sufficiently impure that they could have carried ample amounts of some unrecognized factor to result in the increased growth rates which they produced. Under the conditions of these dietary studies, the rations which contained the fish proteins produced growth superior in all cases to that in which the fish proteins had been replaced at the same level by vitamin-test casein.

In the hypoproteinemia studies, large adult male rats weighing approximately 300 g. were fed the low protein diet employed by P. R. Cannon, E. M. Humphreys, R. W. Wissler, and L. E. Frazier (*J. Clin. Invest.* **23,** *601* (*1944*)) for ninety-five days. At that time the rats had lost about 43 per cent of their original body weight and were divided into three groups equal in respect to the weight loss. The first group was continued on the low protein diet while the second and third groups were maintained on a similar diet except that 9 per cent of the dextrin was replaced by casein or mackerel proteins, respectively. At the end of seven or eight days the hemoglobin concentration, the plasma volume, and plasma concentration of the three groups of rats were determined. It was found that the rats which had received mackerel proteins had gained a little more weight in the recovery period than those that had received casein. The two protein sources were found to be equally effective in producing an increase in the plasma protein concentration and in the plasma volume. However a slightly greater hemoglobin response was observed in the rats which received the diet containing the mackerel protein.

The commercially prepared mackerel protein powder was found by spectrophotometric analysis to be free of vitamin A (H. J. Deuel *et al.*, *J. Nutrition* **31,** *187* (*1946*)), therefore these authors were interested in knowing whether mackerel proteins could replace casein satisfactorily in the diet used for the assay of vitamin A values. Signs of vitamin A deficiency appeared in approximately the same time when the casein was replaced by the same level of mackerel proteins. When limited amounts of vitamin A were fed daily during the bioassay period of four weeks, the growth response observed was significantly greater in the rats which received the mackerel proteins than in those which received casein, providing the rats were of the Sprague-Dawley strain. When rats of the University of California stock colony were used in similar experiments, there was a slightly but not significantly greater growth rate with mackerel proteins. These data were interpreted by these workers to indicate that greater growth was possible with limited amounts of vitamin A when the proteins from mackerel muscle were used instead of casein.

Under the conditions of these experiments, the mackerel proteins appeared to have a greater biologic value than casein. This may be partially explained by the supplementary effects that the individual mackerel proteins would have on each other.

NOTES

Pellagra

August Hirsch ("Handbook of Geographical and Historical Pathology," *Vol. II, p. 217, New Sydenham Society, London (1885)*) compiled the knowledge of the history and distribution of pellagra to the period of his writing.

"The specific noxious thing on which pellagra depends must consist in some factor which is common property to the affected districts only . . . the earliest observers of the disease . . . adopted the opinion that the production of the malady was directly caused by the *use of maize as food* . . .

"(1) Pellagra is *endemic* only in countries where maize is cultivated, and where it constitutes a chief article of diet for the mass of the peasantry . . . in districts lying within the pellagra-areas or directly adjoining them, in which maize, in the above form, is used only exceptionally and does not constitute a material part of the food of the people, the malady is observed rarely or not at all . . . .

"(2) There is not a single fact to prove, or even to hint, that pellagra had been seen in any part of Europe before the introduction of maize . . . .

"(3) A change in the diet, the interdicting of maize altogether and the providing of other kinds of food instead of it, has in many cases effected a complete cure where the malady was in its early stage . . . ."

Professor Hirsch furthermore dismissed the view that pellagra was caused by the generally poor nutritional value of the diet by making the following points: "(1) that, although insufficient food may certainly induce chronic inanition and marasmus, yet the perfectly well-marked morbid state which is distinctive of pellagra is never developed under that influence; (2) that those who fall ill of pellagra not unfrequently have the look of being well nourished at the beginning of the malady, the wasting which occurs in its subsequent course being the effect of organic disease and particularly of the intestinal affection . . . ."

It is true that Hirsch inclined to the view that the so-called pellagra-poison was only in damaged maize. Aside from this, the discussion which is quoted above is in harmony with recent findings in experimental animals which suggest a peculiar role for corn in producing niacin deficiency.

A Record High Source of Ascorbic Acid

Guava at 300 mg. ascorbic acid per 100 g., the fruit of the emblic tree at 800 mg., and rose hips at 1200 to 1700 mg. are extremely rich natural sources of ascorbic acid. It is now reported (C. F. Asenjo and A. R. F. de Guzmán, *Science* **103,** *219 (1946)*) that the West Indian cherry may contain as much as 3300 mg. of ascorbic acid per 100 g. This cherry, weighing about 5 g., is reported as the fruit of the tree commonly called "acerola" in Spanish, and is native to tropical and subtropical America. The variation in ascorbic acid appears to depend principally on the ripeness of the fruit. The green unripe berries contain from 2500 to 3300, medium ripe 2500 to 3000, and the ripe berries 1000 to 2700 mg. per cent. These workers have furthermore isolated and identified pure l-ascorbic acid from the juice of these cherries.

Considering the amounts of ordinary fruits and vegetables that are required to obtain the recommended daily allowance of ascorbic acid, it is intriguing to think that a single one of these berries could supply this allowance.

Apart from the strictly nutritional aspects of the exceptionally rich natural sources of ascorbic acid, is the vexing question of the

possible physiologic basis for such a high concentration. Could a study of the metabolism of rose hips and the West Indian cherry offer any particular advantages in the study of the function of ascorbic acid?

Nutrition and Phagocytosis

In a previous review (*Nutrition Reviews* **2,** *232* (*1944*)) the effect of nutrition on phagocytosis was discussed and reference was made, in particular, to the work of E. Cottingham and C. A. Mills. An additional report by these workers has appeared (*J. Lab. Clin. Med.* **30,** *498* (*1945*)). After measuring phagocytic activity of leucocytes in control rats and in animals fed a diet moderately deficient in protein and the B-vitamins, the diets were reversed and the effects noted. The curves representing phagocytic activity of the two groups crossed one another after one week and replaced one another in another week or two. In all instances phagocytosis was less active in the blood of rats fed the poorer diet. In response to the criticism offered in the above mentioned review, the authors present statistical data which they interpret as supporting the validity of the differences in the phagocyte counts as carried out by them.

Preliminary data are also presented on the study of phagocytosis in human beings. These revealed gradual recovery of phagocytic power in the blood of patients suffering from bacillary dysentery, in 3 ward cases of vitamin deficiency, and in one emaciated patient in whom jejunal resection had been performed. It is difficult to determine, however, what factors led to this improvement in phagocytic activity, for the patients with dysentery were treated with succinylsulfathiazole as well as by improving diet and furnishing supplementary vitamins. In the patients with relatively uncomplicated vitamin deficiencies good recovery of phagocytic function was observed to follow specific vitamin therapy when the latter was the only treatment administered. It is of interest that in 2 patients who died, very low phagocytic function was present at all times.

Army Nutritionists

Former Army nutritionists who desire to return to active duty will be interested in reading Army Service Forces Circular no. 82 dated April 1, 1946. Certain specialists, in fields in which there is a scarcity, may return to active duty for an unlimited length of time or until June 30, 1947, if they fulfill the specified requirements. Upon clarification of proposed plans for formation of a permanent place for nutritionists in the Regular Army, officers who return to active duty under the provisions of this circular will have an opportunity to join the Regular Army on a basis equal with those who remained on active duty. This, plus contemplated legislation dealing with pay, should make an Army career attractive to professional nutritionists.

Recent Nutrition Books

Nutrition Studies in Puerto Rico. Ana Teresa Blanco. Social Science Research Center, University of Puerto Rico. 1946. pp. 96.

Statistical Methods. Fourth Edition. George W. Snedecor. The Collegiate Press, Inc., Ames, Iowa. 1946. pp. 485.

Nutrition and Chemical Growth in Childhood. Vol. II. Icie G. Macy. Charles C. Thomas, Springfield, Ill. 1946. pp. 1460.

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